11/Declaration

PATENT APPLICATION

Docket No. 2001 0878 ORI

UNITED STATES PATENT AND TRADEMARK OFFICE

Re App : Alexander James Wigmore Date: Dec. 9, 2002

S.N. : 09/831,681 Group Art: 1615

Filed : May 10, 2001 Examiner: S.T. Tran

For : CHROMONE ENTERIC RELEASE FORMULATION

Commissioner for Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration Of Alexander James Wigmore

Sir:

I, Alexander James Wigmore, hereby declare as follows:

1. That I am a citizen of the United Kingdom, and an employee of Hewlett Healthcare Limited, West View, The Common, Melbourne, Derbys, DE73 1DH, UK, and am the inventor of the claimed subject matter in the above-identified application for United States Letters Patent;

2. That I have been engaged in the development, assessment, and introduction of pharmaceutical compositions for the treatment of diseases of the respiratory system, eyes, gastrointestinal tract (GIT), and skin for a period of about twenty-six (26) years. Specifically, I have been

engaged in the development of many different formulations of sodium cromoglycate (scg) and related compounds for the treatment of various diseases;

3. That in the course of these activities, I have personally come familiar with the problems encountered with the bioavailability of pharmaceutically active drugs in the GIT;

4. That I have become familiar with the subject matter of the references cited by the Examiner in the course of prosecution, including U.S. Patent No. 6,200,602, and have related the substance of the presently claimed subject matter to the disclosures of the above reference;

5. That the subject matter of the cited reference does not provide the unexpected benefit of the presently claimed compositions, with the reasons being as follows:

The results from using scg in the GIT in the treatment of inflammatory bowel disease and food allergy have been variable, with some authorities reporting good effects and others variable or poor results. Clinical studies have failed to confirm that the oral formulation of scg is adequately effective. Since 1996 my company, Hewlett Healthcare Ltd., has been investigating possible reasons for this lack of efficacy and has discovered that the

problem is a lack of bioavailability of the drug in the GIT.

The lack of bioavailability is caused by a strange physical phenomenon demonstrated by scg in aqueous solutions. At pH 5 to 7 and at concentrations of greater than 7% scg produces a strong and tenacious gel. We discovered that the effect of this gel on a gastrointestinal formulation such as an scg tablet is such that an scg gel coat develops around the tablet preventing further ingress of water and so preventing the tablet from disintegrating and thus preventing the contents from becoming bioavailable. Indeed, the gel is so strong that in our initial tests, when a conventionally manufactured scg tablet was placed in water, the gel prevented the tablet from disintegrating for days and sometimes weeks.

We therefore investigated ways in which the effect of this gelling could be overcome and I unexpectedly discovered that it was necessary to include in the tablet a very high proportion of disintegrant to overcome the cohesive effect of the scg gel and allow the tablet to disintegrate and make the contents bioavailable. I found that the amount of disintegrant (for example microcrystalline cellulose) in the sodium cromoglycate tablet formulation was critical to the dissolution

performance of the tablet. I investigated the effect of varying the proportion of disintegrant to scg in the tablet and found a critical disintegrant to scg ratio of at least 1.2 to 1, more beneficially at least 1.4 or 1.5 to 1, as discussed in the patent application. This is far in excess of the quantity of disintegrant conventionally used in tablets. Normally 15% of the total tablet weight might be disintegrant with an upper normal limit of 20%. The ratio necessary to overcome the gelling forces has in contrast been found to be, for example, at least 47% of the total weight of the tablet (1.4:1 disintegrant to scg ratio). At a 1.76:1 disintegrant to scg ratio disintegrant represents 63% of the total tablet weight.

We would also point out that the mechanism of the disintegration of the tablet should not be confused with the properties of enteric coating. Enteric coating protects a tablet in the acid environment of the stomach enabling it to pass through the stomach intact. Once in the alkaline environment of the small intestine the enteric coat dissolves allowing the tablets to disintegrate but, due to the effect of the scg gel in scg tablet will not dissolve very easily and the critical part of the jejunum will be passed before the tablet is able to release the scg and the substance become bioavailable. This critical ratio

of scg granule to disintegrant ensures the tablet will disintegrate ***quickly*** after the enteric coat has dissolved, which it otherwise would not do. U.S. Patent No. 6,200,602 does not disclose such a critical ratio of disintegrant to scg, nor does it suggest the unexpected drug bioavailability increase effected through the compositions of the present invention.

The blend ratio between the scg and MCC is critical to the performance of the tablet. A tablet with insufficient disintegrant would fail to overcome the gelling effect of scg and the tablet would dissolve slowly.

The dried granules were used to make the following blends. Table 1 lists the blend formulations.

Table 1: Actual Blend Formulations

Blend No.	SCG Granules	MCC	Magnesium Stearate	(Granule-H_2O) : MCC Ratio
1	51.63	47.89	0.58	1:1
2	47.20	52.33	0.48	1:1.2
3	43.39	56.12	0.49	1:1.4
4	40.61	59.39	0.00	1:1.58
5	40.41	59.10	0.49	1:1.58

For the dissolution study, a tablet was placed in the dissolution vessel (paddle) or in the basket. The speed controller was switched on, set to the desired speed and the paddle or basket slowly lowered into the dissolution medium. Dissolution apparatus parameters are listed in Table 2.

A 5ml sample of dissolution medium was removed from the vessel at 5-minute intervals and placed into a labeled sample vial.

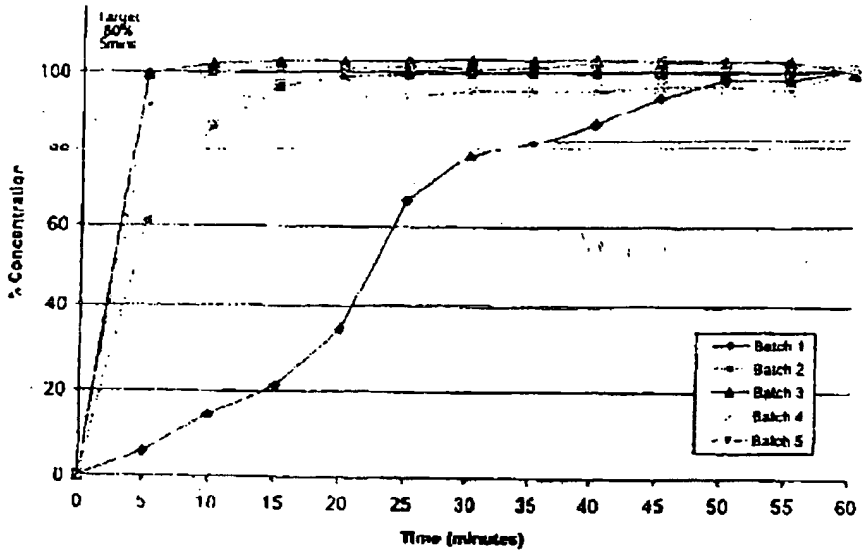
Table 2: Dissolution Apparatus Operating Parameters

Parameter	Details
Apparatus:	Paddle & Basket
Media:	Phosphate Buffer pH 6.8
Temperature:	37°C±0.5°C
Speed:	100rpm±
Test Duration:	60 mins

The HPLC assay method used to analyse the dissolution samples was listed.

The dissolution data for tablets from each blend were normalized to account for the different amounts of scg in each blend. The dissolution profiles of the tablets were then prepared by plotting SCG concentration versus time. Finally, the mean dissolution values were plotted against each other to allow the comparison of each blend.

Study to investigate the effect of various ratios of MCC to SCG and other excipients and their effect on the disintegration of SCG tablets – paddle method



Time	% Sample Concentration				
	Batch 1 —◆—	Batch 2 —◆—	Batch 3 —▲—	Batch 4 --◆--	Batch 5 --●--
0	0	0	0	0	0
5	5.9	60.7	99.7	87.4	92.4
10	14.1	87.1	101.8	94.5	99.7
15	21.3	96.8	102.4	93.8	100.8
20	34.8	99.0	102.5	94.3	100.7
25	66.3	99.3	102.5	94.5	101.3
30	77.4	99.5	102.7	95.6	100.5
35	82.5	99.7	102.6	95.8	100.7
40	87.3	99.5	102.7	95.6	102.3
45	94.2	99.6	102.3	96.6	102.4
50	98.2	99.5	102.2	96.6	102.1
55	98.1	99.6	102.0	95.7	101.9
60	100.1	100.0	99.6	100.5	100.5
Ratio (disintegrant to active)	Ratio 1.07:1	Ratio 1.35:1	Ratio 1.57:1	Ratio 1.76:1 (minus magnesium stearate)	Ratio 1.76:1

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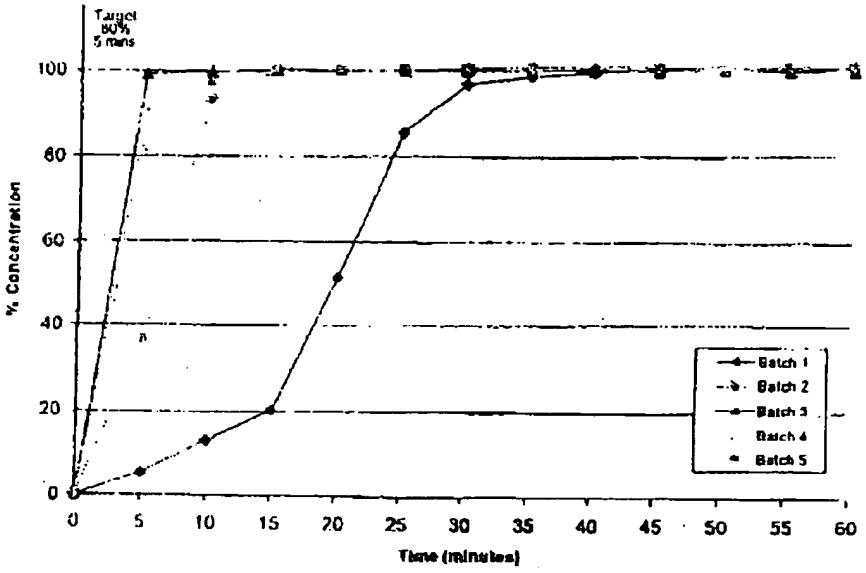
Study to investigate the effect of various ratios of MCC to SCG and other excipients and their effect on the disintegration of SCG tablets – basket method



Time	% Sample Concentration				
	Batch 1 —◆—	Batch 2 ···■···	Batch 3 —▲—	Batch 4 ·····	Batch 5 ···◆···
0	0	0	0	0	0
5	5.2	36.8	99.1	91.4	90.4
10	13.1	93.4	99.7	90.5	97.1
15	20.1	99.8	100.1	99.8	100.4
20	51.2	99.8	100.1	99.7	100.1
25	80.0	100.2	100.1	99.8	100.3
30	97.1	99.9	100.2	99.9	100.4
35	98.5	99.9	100.0	100.0	100.5
40	99.4	99.9	100.2	99.5	100.6
45	99.6	100.1	99.8	100.0	100.6
50	99.8	100.6	100.0	99.9	100.5
55	100.3	99.8	99.9	100.1	100.6
60	100.6	100.4	100.0	100.0	100.7
Ratio (disintegrant to active)	Ratio 1.07:1	Ratio 1.36:1	Ratio 1.57:1	Ratio 1.76:1 (minus magnesium stearate)	Ratio 1.76:1

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SCG Tablet Dissolution Profile

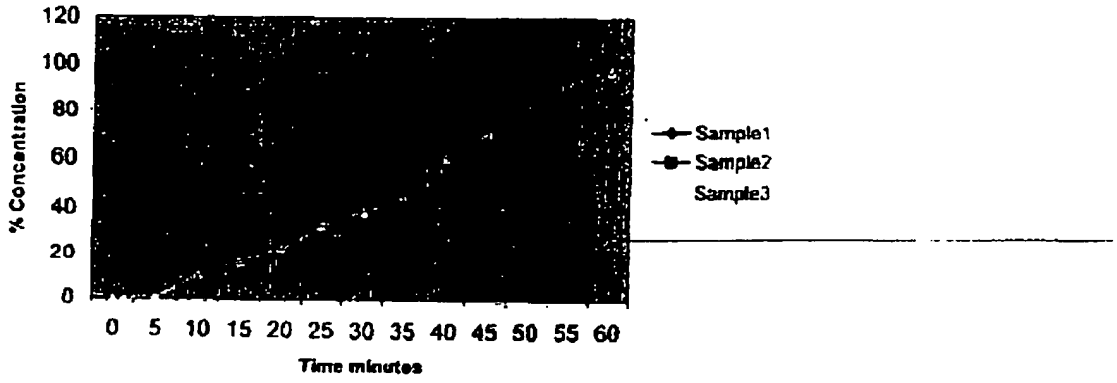
Core Tablets Batch #1

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	8.1	9.1	0.6
10	16.5	15.1	10.6
15	24.9	22.5	16.7
20	33.4	48.3	22.7
25	79.3	66.5	33.2
30	96.2	96.9	39.1
35	101.9	99.6	45.9
40	101.9	99.7	60.3
45	101.8	99.9	70.8
50	102.2	99.9	80.9
55	102.1	99.6	92.9
60	102.1	99.7	98.2

Formulation Ratio: 1:1 SCG Granule 115.85g : Avicel 115.85g + Mag stearate 1.16g

Note: During dissolution it was noted that tablet 3 did not break up ie. kept it's shape until 30-40 minutes

SCG Tablet Dissolution Profile Batch #1



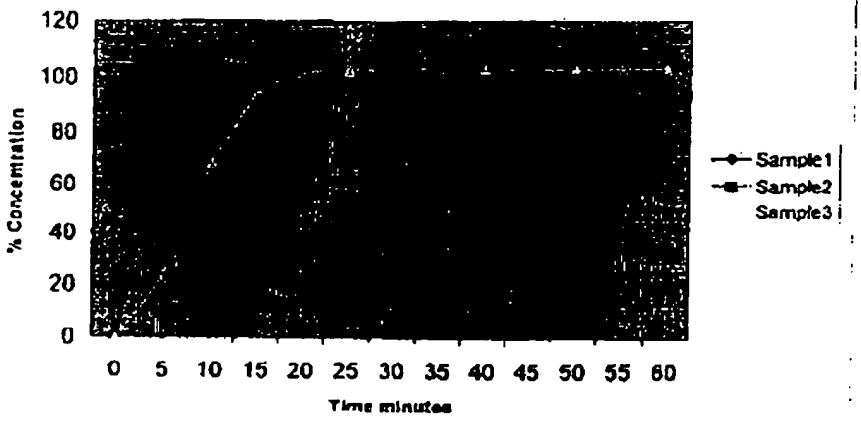
SCG Tablet Dissolution Profile

Core Tablets Batch #2

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	78.4	81	22.9
10	96.1	96.3	68.9
15	97.7	96.7	96.2
20	98	97.1	102
25	97.9	97	102.9
30	98	97.1	103.3
35	98	97.1	103.9
40	98.1	97.1	103.3
45	98	97.4	103.3
50	97.8	97.3	103.5
55	97.5	97.6	103.5
60	98.3	98.2	103.4

Formulation Ratio: 1:1.2 SCG Granule 115.85g : Avicel 139.02g + Mag stearate 1.27g

SCG Tablet Dissolution Profile Batch #2



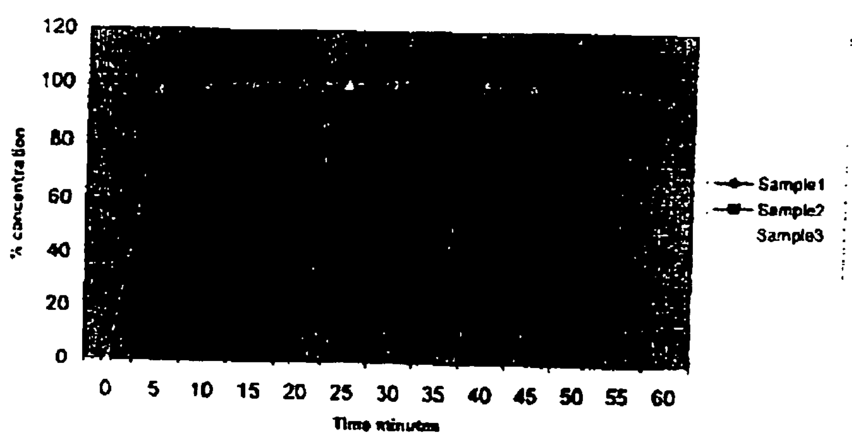
SCG Tablet Dissolution Profile

Core Tablets Batch #3

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	100.2	100.6	98.3
10	102.9	102.8	99.9
15	103.4	103.5	100 4
20	103 3	103.7	100.6
25	103 6	103.2	100.7
30	103 7	103.5	101
35	100.4	103.5	103 8
40	103.9	103.6	100.3
45	103 8	102.4	100.6
50	103.9	102 3	100.5
55	103.8	102.2	100.1
60	103.5	99.6	95.6

Formulation Ratio: [illegible] Granule [illegible] + Mag stearate 1.4g

SCG Tablet Dissolution Profile Batch #3



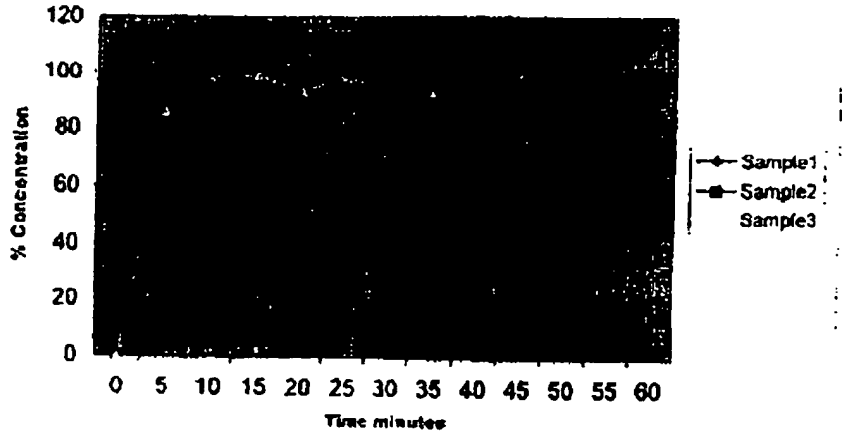
SCG Tablet Dissolution Profile

Core Tablets Batch #4

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
20	93.8	95.7	93.5
25	94.6	90.2	98.6
30	94.6	98.9	93.4
35	95.2	98.7	93.4
40	95.4	94.4	97.7
45	95	95.9	98.8
50	96.3	95.5	98.5
55	92.7	95.8	98.7
60	92.8	101.2	107.6

Formulation Ratio: 1:1.57 SCG Granule 115.85g : Avicel 182.65g + Mag stearate 0.0g

SCG Tablet Dissolution Profile Batch #4



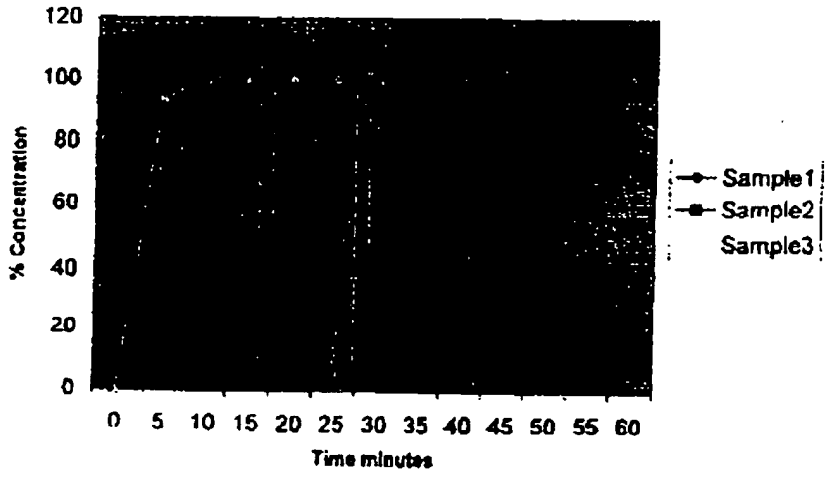
SCG Tablet Dissolution Profile

Core Tablets Batch #5

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
U	U	U	U
5	92.1	91.4	93.7
10	99.7	99.3	100.1
15	100.9	100.8	100.7
20	101.1	100.5	100.6
25	101	102.4	100.5
30	100.6	100.6	100.4
35	100.8	100.5	100.7
40	102.1	103.1	101.7
45	100.6	103.6	103.1
50	100.7	103.1	102.6
55	100.6	103.7	101.4
60	98.9	101.4	101.3

Formulation Ratio: 1:1.47 SCG Granule 115.85g : Avicel 152.65g + Mag stearate 1.5g

SCG Tablet Dissolution Profile Batch #5



6. That based upon my experience, I am fully confident that the Watts et al. (U.S. 6,200,602) reference fails to teach or suggest the unexpedcted beneficial results of the pharmaceutical compositions embodied in the presently pending claims;

7. That this Declaration is given for the purpose of defining and delineating distinctions present in the claimed subject matter of this application from the disclosure available in the reference being relied upon by the Examiner, and that this Declaration is given in support of the patentability of the claims presently under consideration.

I declare under penalty of perjury under the Laws of the United States of America, that the foregoing is true and correct.

Executed on 22nd May, 2003 by:

Alexander James Wigmore.
Alexander J. Wigmore.